



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20850

Date: DEC 27 1995

From: Director, Office of Device Evaluation (HFZ-400)  
Center for Devices and Radiological Health (CDRH)

Subject: Premarket Approval of QLT Phototherapeutics, Inc.  
c/o Hogan & Hartson  
OPTIGUIDE Fiber Optic Diffuser DCYL Series  
Coherent Lambda Plus PDL1 and PDL2  
Photodynamic Lasers  
600 Series Dye Modules (Models 630 and 630 XP) and  
Series 700 and 800 KTP/532 and KTP/YAG  
Surgical Lasers

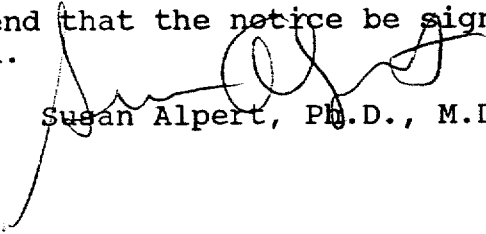
To: The Director, CDRH  
ORA \_\_\_\_\_

ISSUE. Publication of a notice announcing approval of the  
subject PMA's.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

- (1) premarket approval orders for the above  
referenced medical devices (Tab B); and
- (2) the availability of summaries of safety and  
effectiveness data for the devices (Tab C).

RECOMMENDATION. I recommend that the notice be signed and  
published.

  
Susan Alpert, Ph.D., M.D.

Attachments  
Tab A - Notice  
Tab B - Order  
Tab C - S & E Summary

DECISION

Approved \_\_\_\_\_ Disapproved \_\_\_\_\_ Date \_\_\_\_\_

Prepared by Richard P. Felten, CDRH, HFZ-410, December 21, 1995, 594-1307

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. \_\_\_\_\_]

BARD Diagnostic Sciences, Inc.; Premarket Approval of BARD® BTA® Test.

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by BARD Diagnostic Sciences, Inc., Redmond, WA, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of BARD® BTA® Test. After reviewing the recommendation of the Immunology Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on DEC 27 1988, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Peter E. Maxim, Ph.D.

Center for Devices and Radiological Health (HFZ-440)

Food and Drug Administration

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2098 Gaither Road  
Rockville, MD 20850  
301-594-1293.

SUPPLEMENTARY INFORMATION: On June 6, 1994, BARD Diagnostic Sciences, Inc., Redmond, WA, 98052, submitted to CDRH an application for premarket approval of BARD® BTA® Test. The BARD® BTA® rapid latex agglutination test is an in vitro device intended for the qualitative measurement of Bladder Tumor Associated Analytes in human urine to aid in the management of bladder cancer patients.

On September 21, 1995, the Immunology Devices Panel, an FDA advisory panel, reviewed and recommended approval of the application.

On DEC 27 1995, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

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#### OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

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Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. This notice is issued under the Federal Food, Drug, and Cosmetic Act section 520(h), 90 Stat. 554-555, 571 (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: \_\_\_\_\_.

\_\_\_\_\_  
D. Bruce Burlington, M.D.  
Director  
Center for Devices and  
Radiological Health

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

\_\_\_\_\_

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville MD 20856

QLT Phototherapeutics, Inc.  
c/o Mr. Jonathan Kahan  
Hogan & Hartson  
555 Thirteenth Street, Northwest  
Washington, D.C. 20004-1109

DEC 27 1995

Re: P940011  
Coherent PDL1 and PDL2 Lambda Plus Photodynamic Lasers  
Filed: April 13, 1994  
Amended: February 23, March 1,  
and November 13 and 17, 1995

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Coherent PDL1 and PDL2 Lambda Plus Photodynamic Lasers. These devices are indicated for use in Photodynamic Therapy with PHOTOFRIN porfimer sodium as sources of activation of PHOTOFRIN for palliation of patients with completely obstructing esophageal cancer, or patients with partially obstructing esophageal cancer who, in the opinion of their physician cannot be satisfactorily treated with Nd:YAG laser therapy. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL

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Page 2 - Mr. Jonathan Kahan

REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

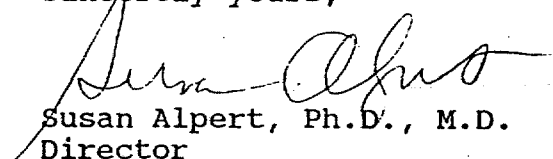
You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Mr. Richard P. Felten at (301) 594-1307.

Sincerely yours,



Susan Alpert, Ph.D., M.D.  
Director  
Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

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## SUMMARY OF SAFETY AND EFFECTIVENESS

### Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers

### 3.1 Introduction

3.1.1	Generic Name:	Argon-Pumped Dye Laser
3.1.2	Device Trade Name:	Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers
3.1.3	Applicant's Name and Address:	QLT Phototherapeutics, Inc.* c/o Mr. Jonathan Kahan Hogan & Hartson 555 Thirteenth Street, N.W. Washington, D.C. 20004-1109

\* a U.S. subsidiary of Quadra Logic Technologies, Inc.,  
Vancouver, BC, V5Z 4H5 Canada

**Laser Manufacturer:** Coherent Medical Group  
**Name and Address:** Coherent, Inc.  
 3270 West Bayshore Road  
 P.O. Box 10122  
 Palo Alto, CA 94303

3.1.4 PMA Number: P940011

### 3.1.5 Panel Recommendation: September 12, 1995

3.1.6 Date of Notice to Applicant: DEC 27 1995

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### **3.2 Indications for Use**

The Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers are intended for use in Photodynamic Therapy (PDT) as sources for the photoactivation of PHOTOFRIN® for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with the Nd:YAG laser.

### **3.3 Description of Device**

The Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers are argon dye lasers which provide guaranteed power output of up to 2.7 Watts (PDL1) and 1.7 Watts (PDL2) of light at 630 nanometers. Each device consists of a continuous wave argon ion laser producing up to 12 Watts, which optically pumps the organic dye contained in the dye lasers. The dyes used in the PDL1 and PDL2 lasers are Kiton Red dye and RH660 dye, respectively. Dosimetry limits, including power and time, are selected by the operator and these are displayed on the control box. Wavelength, which is selectable on the PDL2, is verified by system software. Accuracy of internal power measurement is greater than 80%.

The Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers conform to the requirements of 21 CFR § 1040, Performance Standards for Light Emitting Products.

### **3.4 Alternative Practices and Procedures**

Esophageal cancer often blocks the esophagus and this prevents the patient from swallowing. Most treatments are palliative and focus on surgical methods of maintaining the lumen.

Surgical lasers, such as the continuous wave Nd:YAG laser, are used in the treatment of esophageal cancer. These lasers are used to ablate or otherwise remove cancerous tissue to maintain the lumen. Because they deliver high levels of thermal energy to the site, they also offer some reduction in the risks of hemorrhage.

Because of the high laser energies delivered by continuous wave Nd:YAG lasers, they also create steam and smoke (laser "plume") and tissue charring. This can require smoke evacuators to reduce the potential risks reportedly associated with the plume as well as to minimize odors.

### **3.5 Marketing History**

The Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers have not been marketed in the United States.

The Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers are the result of modifications of an argon dye laser that has been marketed throughout the world since 1985. The device, originally marketed as the Coherent 920 Argon/Dye Laser, was cleared for domestic distribution by the Food and Drug Administration under Premarket Notification K844357 for indications in Ophthalmology and Otology. In June, 1988, the 920 Argon/Dye Laser was cleared for treatment of benign vascular lesions under Premarket Notification K882160. In 1991, the name of the product was changed to the Lambda Plus Argon Dye Laser. Approximately 600 Coherent argon dye lasers have been distributed worldwide since initial distribution in 1985.

Neither the Lambda Plus lasers marketed in other countries nor the Coherent 920 Argon/Dye lasers marketed domestically have ever been withdrawn from market for any reason related to the Safety or Effectiveness of the laser.

### **3.6 Adverse Effects of the Device on Health**

Please refer to the information in NDA 20-451 for full and summarized reports of safety and effectiveness of this combination product.

Adverse effects of the Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers could be related to inappropriate laser powers or improper use. Such situations should not occur if the conditions and instructions for use, as fully described in the PHOTOFRIN® and OPTIGUIDE™ Fiber Optic Diffuser Package Inserts, are followed.

If the laser power should drop so that the light dose delivered to tissue was below that needed to activate PHOTOFRIN®, the treatment would fail. If the power should be greater than expected, so that an excess light dose were delivered to tissue then some areas of adjacent normal tissue, that should have been spared treatment, might be damaged by the PDT effect. At very high laser power levels there would be a risk of damaging the OPTIGUIDE™ Fiber Optic Diffuser if the laser power levels were greater than the OPTIGUIDE™ Fiber Optic Diffuser rated value. This might cause nonuniform output, heating of the diffusing tip and eventual tip destruction. The inclusion of the built-in wavelength meter and use of an external integrated spherical power meter are intended to reduce these possible events.

Please refer to the Summary of Safety and Effectiveness for the OPTIGUIDE™ Fiber Optic Diffuser for additional information and discussion of possible adverse effects of the combination product on health.

Please refer to the attachment for information on Adverse Effects related to the clinical trial as reported in NDA 20-451.

### **3.7 Summary of Studies**

Use of the OPTIGUIDE™ Fiber Optic Diffuser in conjunction with specified lasers to investigate the clinical benefit of PHOTOFRIN® comprises a combination product as defined in the Safe Medical Devices Act of 1990.

Full and summarized reports of the clinical studies of PHOTOFRIN® in the photodynamic therapy of esophageal cancer are presented the PHOTOFRIN® NDA 20-451. See the attachment for a summary of the clinical data from NDA 20-451.

### **3.8 Conclusions Drawn from the Studies**

The in vivo and in vitro nonclinical laboratory studies together with the clinical investigation reported in NDA 20-451 provide valid scientific evidence and provide reasonable assurance that the Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers are safe and effective when used in accordance with their labeling.

The results of the clinical study are reflected in the use instructions accompanying the Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers which refer the user to the PHOTOFRIN® and OPTIGUIDE™ Fiber Optic Diffuser Package Inserts for full information concerning the drug, suitable fiber optic, and laser instructions (power, duration, light dose, etc). The PHOTOFRIN® Package Insert contains a summary of the clinical trial with the appropriate warnings, contraindications, and precautions.

### **3.9 Panel Recommendations**

The Oncology Drug's Advisory Committee, which included as voting members representatives from the Center for Devices and Radiological Health's General and Plastic Surgery Panel, reviewed this application at a public meeting on September 12, 1994 and recommended approval for the Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers as part of the combination device drug system which includes the drug PHOTOFRIN®. The recommendation of approval was for the combination product for use in the palliation of completely obstructing esophageal cancer and partially obstructing esophageal cancer where appropriate. As part of this recommendation, a Phase IV trial will be conducted to determine efficacy and safety in the partially obstructing esophageal cancer patients who were appropriate for this therapy.

### **3.10 FDA Decision**

FDA completed an inspection of the Coherent, Inc.'s manufacturing facility in Palo Alto, California on February 17, 1995. This inspection determined that the manufacturer was in compliance with the Medical Device Good Manufacturing Practice regulation as defined in 21 CFR 820.

FDA concurred with the above recommendation of the Oncology Drugs Advisory Committee regarding the combination drug device product which includes the drug PHOTOFRIN® submitted as NDA 20-451.

### **3.11 Approval Specifications**

Information on the use of the Lambda Plus PDL1 and PDL2 Photodynamic lasers are found in the Lambda Plus PDL1 and PDL2 Operator's Manual. Instructions for use for these lasers as photoactivation sources for PHOTOFRIN® using OPTIGUIDE™ Fiber Optic Diffuser can be found in the drug and fiber optic Package Inserts.

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Return service switch on analog i/o board to its normal position (down).

### *Clinical Applications*

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The Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers are intended for use in Photodynamic Therapy (PDT) as sources for the photoactivation of PHOTOFRIN® for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy. Refer to the PHOTOFRIN® Package Insert for information and instruction for use of the drug. Refer to the OPTIGUIDE™ Package Insert for information and instructions for use of the fiber optic, and information on laser power, duration, and light dose. \*

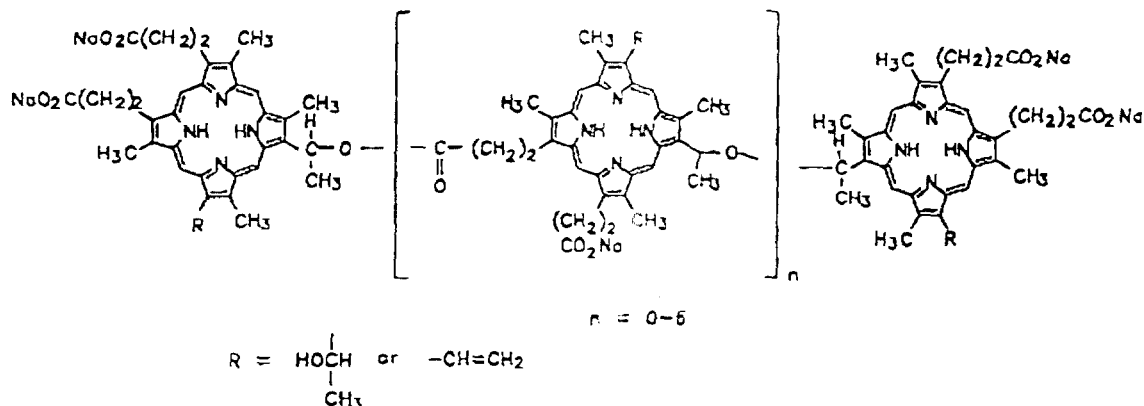
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PHOTOFRIN® porfimer sodium

U.S. Package Insert

## PHOTOFRIN® (sterile porfimer sodium)

### DESCRIPTION

PHOTOFRIN® porfimer sodium is a photosensitizing agent used in the photodynamic therapy (PDT) of tumors. Following reconstitution of the freeze-dried product with 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), it is injected intravenously. This is followed 40–50 hours later by illumination of the tumor with laser light (630 nm wavelength). PHOTOFRIN® is not a single chemical entity; it is a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units. It is a dark red to reddish brown cake or powder. Each vial of PHOTOFRIN® contains 75 mg of porfimer sodium as a sterile freeze-dried cake or powder. Hydrochloric Acid and/or Sodium Hydroxide may be added during manufacture to adjust pH. There are no preservatives or other additives. The structural formula below is representative of the components present in PHOTOFRIN®.



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PHOTOFRIN® porfimer sodium

U.S. Package Insert

## CLINICAL PHARMACOLOGY

### Pharmacology

The cytotoxic and antitumor actions of PHOTOFRIN® are light and oxygen dependent. Photodynamic therapy (PDT) with PHOTOFRIN® is a two-stage process. The first stage is the intravenous injection of PHOTOFRIN®. Clearance from a variety of tissues occurs over 40–72 hours, but tumor, skin, and organs of the reticuloendothelial system (including liver and spleen) retain PHOTOFRIN® for a longer period. Illumination with 630 nm wavelength laser light constitutes the second stage of therapy. Tumor selectivity in treatment occurs through a combination of selective retention of PHOTOFRIN® and selective delivery of light. Cellular damage caused by PHOTOFRIN® PDT is a consequence of the propagation of radical reactions. Radical initiation may occur after PHOTOFRIN® absorbs light to form a porphyrin excited state. Spin transfer from PHOTOFRIN® to molecular oxygen may then generate singlet oxygen. Subsequent radical reactions can form superoxide and hydroxyl radicals. Tumor death also occurs through ischemic necrosis secondary to vascular occlusion that appears to be partly mediated by thromboxane A<sub>2</sub> release. The laser treatment induces a photochemical, not a thermal, effect.

### Pharmacokinetics

Following a 2 mg/kg dose of porfimer sodium to 4 male cancer patients, the average peak plasma concentration was  $15 \pm 3 \mu\text{g/mL}$ , the elimination half-life was  $250 \pm 285$  hour, the steady-state volume of distribution was  $0.49 \pm 0.28$  L/kg, and the total plasma clearance was  $0.051 \pm 0.035$  mL/min/kg. The mean plasma concentration at 48 hours was  $2.6 \pm 0.4 \mu\text{g/mL}$ . The influence of impaired hepatic function on PHOTOFRIN® disposition has not been evaluated.

PHOTOFIRIN® was approximately 90% protein bound in human serum, studied in vitro. The binding was independent of concentration over the concentration range of 20–100  $\mu\text{g/mL}$ .

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## Clinical Studies

PDT with PHOTOFRIN® was utilized in a multicenter, single-arm study in 17 patients with completely obstructing esophageal carcinoma. Each course of PDT with PHOTOFRIN® consisted of one injection of the drug (2 mg/kg administered as a slow intravenous injection over 3–5 minutes) followed by up to two nonthermal laser light applications (630 nm administered at a dose of 300 J/cm of tumor), the first application of light occurring 40–50 hours after injection. Debridement of residua was performed via endoscopy 96–120 hours after injection, after which any residual tumor could be retreated with a second laser light application at the same dose used for the initial treatment. Additional courses of PDT with PHOTOFRIN® were allowed after 1 month, up to a total of 3. Assessments were made at 1 week and 1 month after the last treatment procedure. As shown in Table 1, after a single course of therapy, 94% of patients obtained an objective tumor response and 76% of patients experienced some palliation of their dysphagia. On average, before treatment these patients had difficulty swallowing liquids, even saliva. After one course of therapy, there was a statistically significant improvement in mean dysphagia grade (1.5 units,  $p < 0.05$ ) and 13 of 17 patients could swallow liquids without difficulty 1 week and/or 1 month after treatment. Based on all courses, three patients achieved a complete tumor response (CR). In two of these patients, the CR was documented only at Week 1 as they had no further assessments. The third patient achieved a CR after a second course of therapy, which was supported by negative histopathology and maintained for the entire follow-up of 6 months.

Of the 17 treated patients, 11 (65%) received clinically important benefit from PDT. Clinically important benefit was defined hierarchically by obtaining a complete tumor response (3 patients), achieving normal swallowing (2 patients went from Grade 5 dysphagia to Grade 1), or achieving a dramatic improvement of two or more grades of dysphagia with minimal adverse reactions (6 patients). The median duration of benefit in these patients was 69+ days. Duration of benefit was calculated only for the period with documented evidence of improvement. All of these patients were still in response at their last assessment and, therefore, the estimate of 69 days is conservative. The median survival for these 11 patients was 115 days.

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**TABLE 1. Course 1 Efficacy Results in Patients with Completely Obstructing Esophageal Cancer**

	PDT n = 17
<b>IMPROVEMENT<sup>a</sup> IN DYSPHAGIA</b> (% of Patients)	
Week 1	71%
Month 1	47%
Any assessment <sup>b</sup>	76%
<b>MEAN DYSPHAGIA GRADE<sup>c</sup> AT BASELINE</b>	
	4.6
<b>MEAN IMPROVEMENT<sup>c</sup> IN DYSPHAGIA GRADE (units)</b>	
Week 1	1.4
Month 1	1.5
<b>OBJECTIVE TUMOR RESPONSE<sup>d</sup></b> (% of Patients)	
Week 1	82%
Month 1	35% <sup>e</sup>
Any assessment <sup>b</sup>	94%
<b>MEAN NUMBER OF LASER APPLICATIONS PER PATIENT</b>	
	1.4

<sup>a</sup> Patients with at least a one-grade improvement in dysphagia grade

<sup>b</sup> Week 1 or Month 1

<sup>c</sup> Dysphagia Scale: Grade 1 = normal swallowing, Grade 2 = difficulty swallowing some hard solids; can swallow semisolids, Grade 3 = unable to swallow any solids; can swallow liquids, Grade 4 = difficulty swallowing liquids, Grade 5 = unable to swallow saliva.

<sup>d</sup> CR+PR, CR = complete response (absence of endoscopically visible tumor), PR = partial response (appearance of a visible lumen)

<sup>e</sup> Eight of the 17 treated patients did not have assessments at Month 1.

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## INDICATIONS AND USAGE

Photodynamic therapy with PHOTOFRIN® is indicated for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.

## CONTRAINDICATIONS

PHOTOFRIN® is contraindicated in patients with porphyria or in patients with known allergies to porphyrins.

PDT is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula.

PDT is contraindicated in patients with tumors eroding into a major blood vessel.

## WARNINGS

If the esophageal tumor is eroding into the trachea or bronchial tree, the likelihood of tracheoesophageal or bronchoesophageal fistula resulting from treatment is sufficiently high that PDT is not recommended.

Following injection with PHOTOFRIN® precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light (see PRECAUTIONS).

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PHOTOFRIN® porfimer sodium

U.S. Package Insert

## PRECAUTIONS

### Information for Patients

All patients who receive PHOTOFRIN® will be photosensitive and must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, etc.) for 30 days. The photosensitivity is due to residual drug which will be present in all parts of the skin. Exposure of the skin to ambient indoor light is beneficial because the remaining drug will be inactivated gradually and safely through a photobleaching reaction. Therefore, patients should not be kept in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light. The level of photosensitivity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the patient should test it for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. If no photosensitivity reaction (erythema, edema, blistering) occurs within 24 hours, the patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If some photosensitivity reaction occurs with the limited skin test, the patient should continue precautions for another 2 weeks before retesting. The tissue around the eyes may be more sensitive, and therefore, it is not recommended that the face be used for testing. If patients travel to a different geographical area with greater sunshine, they should retest their level of photosensitivity. UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light.

Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in patients who received PHOTOFRIN®. For 30 days, when outdoors, patients should wear dark sunglasses which have an average white light transmittance of <4%.

As a result of PDT treatment, patients may complain of substernal chest pain because of inflammatory responses within the area of treatment. Such pain may

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be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Women of childbearing potential should practice an effective method of contraception during therapy (see Pregnancy).

### **Drug Interactions**

There have been no formal interaction studies of PHOTOFRIN® and any other drugs. However, it is possible that concomitant use of other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics, and griseofulvin) would have the potential to increase the photosensitivity reaction.

PHOTOFRIN® PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many drugs could influence the effects of PDT, possible examples of which are described below. There are no human data that support or rebut these possibilities.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, b-carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PHOTOFRIN® PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A<sub>2</sub> inhibitors, could decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT may decrease the efficacy of the treatment.

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

No long-term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN®. In vitro, PHOTOFRIN® PDT, with or without S9 activation, did not cause mutations in the Ames test, nor did it cause chromosome aberrations or

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U.S. Package Insert

mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. PHOTOFRIN® caused < 2-fold, but significant, increases in sister chromatid exchange in CHO cells irradiated with visible light and a 3-fold increase in Chinese hamster lung fibroblasts irradiated with near UV light. PHOTOFRIN® PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. PHOTOFRIN® PDT caused a light-dose dependant increase in DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. The mutagenicity of PHOTOFRIN® without light has not been adequately determined. In vivo, PHOTOFRIN® did not cause chromosomal aberrations in the mouse micronucleus test

PHOTOFIRIN® given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m<sup>2</sup> basis) before conception and through Day 7 of pregnancy caused no impairment of fertility. In this study, long-term dosing with PHOTOFRIN® caused discoloration of testes and ovaries and hypertrophy of the testes. PHOTOFRIN® also caused decreased body weight in the parent rats.

#### **Pregnancy: Pregnancy Category C**

There are no adequate and well-controlled studies in pregnant women. PHOTOFRIN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PHOTOFRIN® given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m<sup>2</sup> basis) for 10 days caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, decreased litter size, delayed ossification, and reduced fetal weight. PHOTOFRIN® caused no major malformations when given to rabbits intravenously during organogenesis at 4 mg/kg/d (0.65 times the clinical dose on a mg/m<sup>2</sup> basis) for 13 days. This dose caused maternal toxicity resulting in increased resorptions, decreased litter size, and reduced fetal body weight.

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PHOTOFRIN® given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m<sup>2</sup> basis) for at least 42 days caused a reversible decrease in growth of offspring. Parturition was unaffected.

### **Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PHOTOFRIN®, women receiving PHOTOFRIN® must not breast feed.

### **Pediatric Use**

Safety and effectiveness in children have not been established.

### **Use in Elderly Patients**

Almost 80% of the patients treated with PDT using PHOTOFRIN® in clinical trials were over 60 years of age. There was no apparent difference in effectiveness or safety in these patients compared to younger people. Dose modification based upon age is not required.

## **ADVERSE REACTIONS**

Systemically induced effects associated with PDT with PHOTOFRIN® consist of photosensitivity and mild constipation. All patients who receive PHOTOFRIN® will be photosensitive and must observe precautions to avoid sunlight and bright indoor light (see PRECAUTIONS). Photosensitivity reactions (mostly mild erythema on the face and hands) occurred in approximately 20% of patients treated with PHOTOFRIN®.

Most toxicities associated with this therapy are local effects seen in the region of illumination and occasionally in surrounding tissues. The local adverse reactions are characteristic of an inflammatory response induced by the photodynamic effect.

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## Esophageal Carcinoma

The following adverse events were reported in at least 5% of patients treated with PHOTOFRIN® PDT, who had completely or partially obstructing esophageal cancer. Table 2 presents data from 88 patients who received the currently marketed formulation. The relationship of many of these adverse events to PDT with PHOTOFRIN® is uncertain.

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**TABLE 2. Adverse Events Reported in 5% or More of Patients with  
Obstructing Esophageal Cancer  
(Page 1 of 3)**

Number (%) of Patients			
BODY SYSTEM/ Adverse Event		PDT with PHOTOFRIN® n = 88	
Patients with at Least One Adverse Event		84	(95)
AUTONOMIC NERVOUS SYSTEM			
Hypertension		5	(6)
Hypotension		6	(7)
BODY AS A WHOLE			
Asthenia		5	(6)
Back pain		10	(11)
Chest pain		19	(22)
Chest pain (substernal)		4	(5)
Edema generalized		4	(5)
Edema peripheral		6	(7)
Fever		27	(31)
Pain		19	(22)
Surgical complication		4	(5)
CARDIOVASCULAR			
Cardiac failure		6	(7)
GASTROINTESTINAL			
Abdominal pain		18	(20)
Constipation		21	(24)
Diarrhea		4	(5)
Dyspepsia		5	(6)
Dysphagia		9	(10)
Eructation		4	(5)
Esophageal edema		7	(8)

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**TABLE 2. Adverse Events Reported in 5% or More of Patients with  
Obstructing Esophageal Cancer**  
(Page 2 of 3)

Number (%) of Patients	
BODY SYSTEM/ Adverse Event	PDT with PHOTOFRIN® n = 88
GASTROINTESTINAL (continued)	
Esophageal tumor bleeding	7 (8)
Esophageal stricture	5 (6)
Esophagitis	4 (5)
Hematemesis	7 (8)
Melena	4 (5)
Nausea	21 (24)
Vomiting	15 (17)
HEART RATE/RHYTHM	
Atrial fibrillation	9 (10)
Tachycardia	5 (6)
METABOLIC & NUTRITIONAL	
Dehydration	6 (7)
Weight decrease	8 (9)
PSYCHIATRIC	
Anorexia	7 (8)
Anxiety	6 (7)
Confusion	7 (8)
Insomnia	12 (14)
RED BLOOD CELL	
Anemia	28 (32)
RESISTANCE MECHANISM	
Moniliasis	8 (9)

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**TABLE 2. Adverse Events Reported in 5% or More of Patients with Obstructing Esophageal Cancer**  
(Page 3 of 3)

Number (%) of Patients	
BODY SYSTEM/ Adverse Event	PDT with PHOTOFRIN® n= 88
<b>RESPIRATORY</b>	
Coughing	6 (7)
Dyspnea	18 (20)
Pharyngitis	10 (11)
Pleural effusion	28 (32)
Pneumonia	16 (18)
Respiratory insufficiency	9 (10)
Tracheoesophageal fistula	5 (6)
<b>SKIN &amp; APPENDAGES</b>	
Photosensitivity reaction	17 (19)
<b>URINARY</b>	
Urinary tract infection	6 (7)

Location of the tumor was a prognostic factor for three adverse events: upper-third of the esophagus (esophageal edema), middle-third (atrial fibrillation), and lower-third, the most vascular region (anemia). Also, patients with large tumors (>10 cm) were more likely to experience anemia. Two of 17 patients with complete esophageal obstruction from tumor experienced esophageal perforations which were considered to be possibly treatment associated; these perforations occurred during subsequent endoscopies.

Serious and other notable adverse events observed in less than 5% of PDT-treated patients in the clinical studies include the following; their relationship to therapy is uncertain. In the gastrointestinal system, esophageal perforation, gastric ulcer, gastrointestinal hemorrhage, ileus, jaundice, and peritonitis have occurred. Sepsis has been reported occasionally. Cardiovascular events have included angina

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pectoris, bradycardia, cerebrovascular disorder, congestive heart failure, myocardial infarction, sick sinus syndrome, and supraventricular tachycardia. Respiratory events of bronchitis, bronchospasm, laryngotracheal edema, pneumonitis, pulmonary hemorrhage, pulmonary edema, respiratory failure, and stridor have occurred. The temporal relationship of some gastrointestinal, cardiovascular and respiratory events to the administration of light was suggestive of mediastinal inflammation in some patients. Vision-related events of abnormal vision, diplopia, eye pain and photophobia have been reported.

### **Laboratory Abnormalities**

PDT with PHOTOFRIN® may result in anemia due to tumor bleeding. No consistent effects were observed for other parameters.

## **OVERDOSAGE**

### **PHOTOFRIN® Overdose**

There is no information on overdosage situations involving PHOTOFRIN®. Effects of overdosage on the duration of photosensitivity are unknown. Laser treatment should not be given if an overdose of PHOTOFRIN® is administered. In the event of an overdose, patients should protect their eyes and skin from direct sunlight or bright indoor lights for 30 days. At this time, patients should test for residual photosensitivity (see PRECAUTIONS). PHOTOFRIN® is not dialyzable.

### **Overdose of Laser Light Following PHOTOFRIN® Injection**

There is no information on overdose of laser light following PHOTOFRIN® injection in patients with esophageal carcinoma. Increased symptoms and damage to normal tissue might be expected following an overdose of light.

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## DOSAGE AND ADMINISTRATION

Photodynamic therapy with PHOTOFRIN® is a two-stage process requiring administration of both drug and light. Practitioners should be trained in the safe and efficacious treatment of esophageal cancer using photodynamic therapy with PHOTOFRIN® and associated light delivery devices. The first stage of PDT is the intravenous injection of PHOTOFRIN® at 2 mg/kg. Illumination with laser light 40–50 hours following injection with PHOTOFRIN® constitutes the second stage of therapy. A second laser light application may be given 96–120 hours after injection, preceded by gentle debridement of residual tumor (see Administration of Laser Light). In clinical studies, debridement via endoscopy was required 2 days after the initial light application. However, experience has indicated that mandatory debridement may not be necessary due to natural sloughing action in the esophagus and may, in fact, needlessly traumatize the area.

Patients may receive a second course of PDT a minimum of 30 days after the initial therapy; up to three courses of PDT (each separated by a minimum of 30 days) can be given. Before each course of treatment, patients should be evaluated for the presence of a tracheoesophageal or bronchoesophageal fistula (see CONTRAINDICATIONS).

### PHOTOFRIN® Administration

PHOTOFRIN® should be administered as a single slow intravenous injection over 3 to 5 minutes at 2 mg/kg body weight. Reconstitute each vial of PHOTOFRIN® with 31.8 mL of either 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), resulting in a final concentration of 2.5 mg/mL. Shake well until dissolved. Do not mix PHOTOFRIN® with other drugs in the same solution. PHOTOFRIN®, reconstituted with 5% Dextrose Injection (USP) or with 0.9% Sodium Chloride Injection (USP), has a pH in the range of 7 to 8. PHOTOFRIN® has been formulated with an overage to deliver the 75 mg labeled quantity. The reconstituted product should be protected from bright light and used immediately. Reconstituted PHOTOFRIN® is an opaque solution, in which detection of particulate matter by visual inspection is extremely difficult. Reconstituted PHOTOFRIN®, however, like all parenteral drug products, should be inspected visually for

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particulate matter and discoloration prior to administration whenever solution and container permit.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, care must be taken to protect the area from light. There is no known benefit from injecting the extravasation site with another substance.

### **Administration of Laser Light**

Initiate 630 nm wavelength laser light delivery to the patient 40–50 hours following injection with PHOTOFRIN®. A second laser light treatment may be given as early as 96 hours or as late as 120 hours after the initial injection with PHOTOFRIN®. No further injection of PHOTOFRIN® should be given for such retreatment with laser light. Before providing a second laser light treatment, the residual tumor should be debrided. Vigorous debridement may cause tumor bleeding.

The laser system must be approved for delivery of a stable power output at a wavelength of  $630 \pm 3$  nm. Light is delivered to the tumor by cylindrical OPTIGUIDE™ fiber optic diffusers passed through the operating channel of an endoscope. Instructions for use of the fiber optic and the selected laser system should be read carefully before use. Photoactivation of PHOTOFRIN® is controlled by the total light dose delivered. In the treatment of esophageal cancer, a light dose of 300 joules/cm of tumor length should be delivered. OPTIGUIDE™ cylindrical diffusers are available in several lengths. The choice of diffuser tip length depends on the length of the tumor. Diffuser length should be sized to avoid exposure of nonmalignant tissue to light and to prevent overlapping of previously treated malignant tissue. The total power output at the fiber tip is set to deliver the appropriate light dose using exposure times of 12 minutes and 30 seconds. Refer to the OPTIGUIDE™ instructions for use for complete instructions concerning the fiber optic diffuser.

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**HOW SUPPLIED**

PHOTOFRIN® (sterile porfimer sodium) is supplied as a freeze-dried cake or powder as follows:

NDC XXXX-XXXX-XX — 75 mg vial

PHOTOFRIN® freeze-dried cake or powder should be stored at Controlled Room Temperature 15–30°C (59–86°F).

Distributed by

DIST. LOGO

[Name and address to be inserted when finalized]

Manufactured by

LEDERLE PARENTERALS, INC.  
Carolina, Puerto Rico 00987

for

QLT LOGO

QLT PHOTOTHERAPEUTICS INC.  
Seattle, WA 98101

**Spills and Disposal**

Spills of PHOTOFRIN® should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light; use of rubber gloves and eye protection is recommended. All contaminated materials should be disposed of in a polyethylene bag in a manner consistent with local regulations.

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### **Accidental Exposure**

PHOTOFRIN® is neither a primary ocular irritant nor a primary dermal irritant. However, because of its potential to induce photosensitivity, PHOTOFRIN® might be an eye and/or skin irritant in the presence of bright light. It is important to avoid contact with the eyes and skin during preparation and/or administration. As with therapeutic overdosage, any overexposed person must be protected from bright light.